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Controlled rate thermogravimetry of inclusion complexes of cholic acid with fluorobenzyl alcohols: molecular adsorption on crystal surfaces

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Abstract

Controlled rate thermogravimetry was applied to the several crystalline inclusion complexes of cholic acid with 2-, 3- and 4-fluorobenzyl alcohol. The purpose of this was to investigate the previous experimental results of these complexes using conventional thermogravimetry which indicated that the weight loss was rather more than the theoretical prediction based on a host–guest ratio elucidated by X-ray crystallography. The results, together with X-ray measurements, indicate that this "excess" weight loss results from the adsorption of the fluorobenzyl alcohols on the crystal surfaces. Further examination of these results revealed the substance release mechanism: the adsorbed molecules are first released, followed by the release of the included guests when the crystals were heated. These phenomena may be attributed to the properties of the CH_2OH group in the fluorobenzyl alcohols.

Keywords: Cholic acid; Controlled rate thermal analysis; Inclusion complex

1. Introduction

After the establishment of thermal analysis techniques, many measurements have been performed to study the thermal properties of molecular complexes. Thermo-

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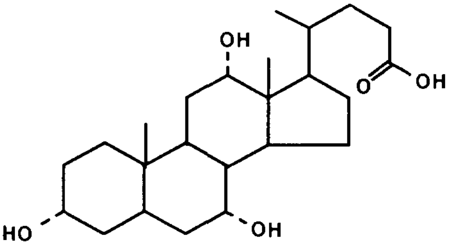
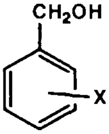
gravimetry (TG), one of the thermal analysis methods, has been utilized to investigate the thermal stability and thermal decomposition mechanisms of complexes [1–3]. To date we and other workers have studied the inclusion complexes of cholic acid (CA), a naturally occurring bile acid and its derivative, with organic guests using conventional TG [4–6]. The resolution of the TG curves obtained, however, was not fully satisfactory, and with the exception of the host–guest ratio, precise information has not hitherto been obtained. Such obscure TG curves mainly result from the fact that conventional TG subjects samples to a uniform heating rate [7].

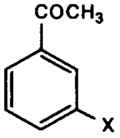
Recently we performed TG on the crystalline complexes of CA with 2-, 3- and 4-fluorobenzyl alcohol (2-, 3- and 4-FBzOH, respectively, using a conventional TG system (see scheme). The results showed that, in each analysis, the weight loss was rather more than the theoretical prediction based on a host–guest ratio elucidated by the X-ray method. Such a phenomenon has not been observed in the other CA complexes. This system, however, gave no information about this "excess" weight loss because of the poor resolution. Therefore, controlled-rate thermogravimetry (CRTG) [8] was applied to these complexes to investigate the "excess" weight loss. Here we report that the "excess" loss results from the adsorption of the fluorobenzyl alcohols on the crystal surfaces through weak interaction. In addition, we discuss the substance release mechanism and the role of the functional groups of the fluorobenzyl alcohols and CA in the adsorption.



cholic acid



X = H benzyl alcohol
= F at *o*-position 2-fluorobenzyl alcohol
= F at *m*-position 3-fluorobenzyl alcohol
= F at *p*-position 4-fluorobenzyl alcohol



X = H acetophenone
= F 3'-fluoroacetophenone

Scheme 1

2. Experimental

2.1. Materials

The crystalline inclusion complexes of CA with benzyl alcohol (BzOH), 2- and 3-FBzOH were obtained by the absorption method, i.e. soaking pure CA crystals in liquid guest at ambient temperature for a few days [9]. The crystals were obtained as colorless needles and the crystal size was approx. 0.5 × 0.5 × 3.0 mm. The crystalline complexes of CA with 4-fluorobenzyl alcohol (4-FBzOH), acetophenone (AP) and 3′-fluoroacetophenone (3′-FAP) were prepared as follows: a solution of CA (0.3 g) in 4-FBzOH, AP or 3′-FAP (2 cm^3) was kept at room temperature for about 12 h and crystals of the 1:1 inclusion complex were obtained as colorless needles (0.5 × 0.5 × 2.0 mm, CA-4-FBzOH) or prisms (1.0 × 0.5 × 3.0 mm, CA-AP and -3′-FAP) [9–11].

2.2. Thermal measurements

CRTG of the CA-2-, -3- and -4-FBzOH complexes, and conventional TG of the CA-3-FBzOH complex were carried out using a Rigaku TAS300. Samples, well-dried on filter paper, were heated from ambient temperature to the temperature specified by the heating program in nitrogen flowing at 100 ml min^{-1}. The overall duration of all the experiments was about 8 h. Conventional TG was carried out with a Seiko TG/DTA 220. Samples were heated from ambient temperature to the temperature specified by the heating program in nitrogen flowing at 100 ml min^{-1}. The heating rate was 3 K min^{-1}. TG/mass spectrometry (MS) analyses were measured with a TG/MS system consisting of a Rigaku TAS200 and Hewlett Packard HP5971A. The well-dried sample (CA-3-FBzOH) of 15.160 mg was heated from ambient temperature to 523 K at 10 K min^{-1} in helium flowing at 150 ml min^{-1}.

2.3. X-ray diffraction measurements

The lattice parameters of the crystal of the CA-3-FBzOH complex heated to 60°C using CRTG were determined using a Rigaku AFC7R diffractometer with graphite-monochromated Cu-Kα(λ = 1.54178 Å) radiation at 293 K. The X-ray microdiffraction patterns of the original and heated crystals of the CA-3-FBzOH complex were obtained with a Rigaku RINT2000 PSPC/MDG microdiffractometer using a collimeter of 100 nm diameter.

3. Results and discussion

Fig. 1, curve A shows the TG curves for the CA-3-FBzOH complex obtained using CRTG and conventional TG. The experimental and theoretical weight loss data are shown in Table 1. It can be seen that gradual decomposition occurs from 323 to 473 K in the conventional TG curve. This weight loss may be explained by the gradual release

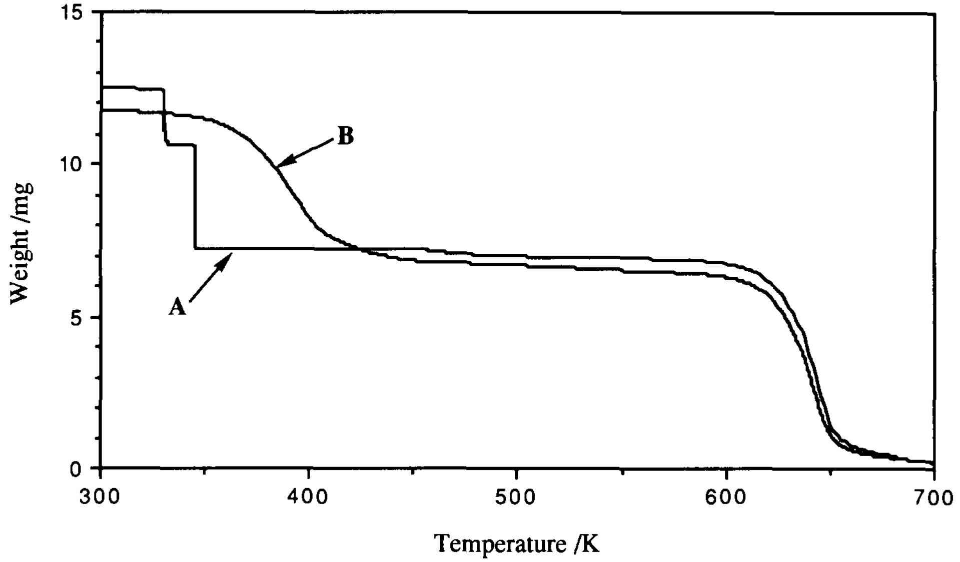


Fig. 1. TG plots using CRTG (A) and conventional TG (B) of the CA-3-FBzOH complex. (A) sample weighing 12.470 mg was heated from ambient temperature to 330 K at a heating rate of 5 K $\min^{-1}$ and the sample was heated using CRTG above 330 K. The parameters used were TC (time constant) = 3, S (sensitivity) = 6, R (resolution) = 3 and T_i (initial temperature of CRTG) = 57 [12]. (B) Sample weighing 11.750 mg was heated from ambient temperature to 723 K at the heating rate of 5 K $\min^{-1}$.

Table 1
Weight loss[a] and residual weight of CA-3-FBzOH (in wt%)

	Experimental		
	Conventional TG	CRTG	Theoretical
Total loss	43·6	42·3	31·7
1st loss	–	15·0[b]	–
2nd loss	–	27·3[c]	–
Residue	56·4	57·7	68·3

[a] Up to 473 K.
[b,c] Occurred at 330 and 346 K, respectively.

of 3-FBzOH. Further weight loss which occurs above 573 K and completes above 673 K is due to the decomposition of CA. It is noteworthy that the weight loss is rather more than the theoretical prediction based on a host–guest ratio of 1:1.5 elucidated by the X-ray method [9]. CRTG gives better separation of these successive weight losses. Two rapid weight losses commence at 330 and 346 K, respectively and are completed within 1 K. The total loss is rather more than the theoretical prediction, similarly to the conventional TG curve. Here we assumed that this "excess" weight loss is due to the adsorbed molecules on the crystal surfaces, since the theoretical value agrees well with the value (32.1% = 27.3/(27.3 + 57.7)) based on the assumption that the release of the included guest is attributed to only the second loss. To identify the gaseous substances evolved during the heating, TG/MS was applied. This analysis indicates that both the substances evolved at the first and second weight losses are 3-FBzOH molecules. Thus these results suggest that 3-FBzOH molecules adsorb onto the surfaces. A similar TG curve was observed when the crystals of the CA-2- and -4-FBzOH complexes were heated using CRTG. Two rapid weight losses commence at 331 and 374 K and the percentage of the second weight loss relative to the residual weight (23.3 wt%) agrees well with the theoretical value (23.6 wt%) based on a host–guest ratio of 1:1 [9] when the CA-4-FBzOH crystals were heated. Similarly this percentage (22.6 wt%) coincides well with the theoretical value (23.6 wt%) in the case of the CA-2-FBzOH complex. Consequently, these results indicate that 2- and 4-FBzOH molecules are adsorbed on the crystal surfaces.

To confirm that only the adsorbed molecules on the surfaces are released at the first weight loss and that the included guests did not release at this point, we determined the lattice parameters of the CA-3-FBzOH crystal heated until 333 K using CRTG, comparing the parameters with those of the original crystal. Table 2 shows the lattice parameters of the original and heated crystals, indicating that the heated crystal has almost the same parameters as those of the original. These measurements were made on a single crystal. To further confirm the identity, the X-ray diffraction patterns of the small circular area of the original and heated crystals were measured. As seen in Fig. 2, the diffraction pattern of the heated crystals is essentially the same as that of the original. The slight changes may result from the unevenness of the sample. If not only the adsorbed molecules but also the included guests were released, the crystal lattice of the heated crystals would not maintain the original pattern. Thus these X-ray measurements show that the crystal structure does not change at the first weight loss, which, together with the thermal and mass spectrographic analyses, indicate that the first weight loss is due to only the adsorbed 3-FBzOH molecules.

As mentioned above, we and other workers have performed thermal analyses on several CA inclusion complexes, finding that the total weight loss up to 473 K agrees well with the theoretical value in almost all the complexes. In other words, these results have indicated that the guest molecules do not bind to the crystal surfaces, unlike 3-FBzOH. Therefore, it is clear that the first weight loss is merely due to the wetness of the crystals in the present analyses.

Table 2
Lattice parameter of the original CA-3-FBzOH inclusion complex crystal and of the crystal heated to 333 K using CRTG

Crystal	a/Å	b/Å	c/Å	β/°	V/Å^3
Original[a]	13.459(4)	8.485(4)	28.512(5)	101.30(2)	3193(1)
Heated	13.412(4)	8.503(4)	28.546(6)	101.23(2)	3193(2)

[a] Ref. [9].

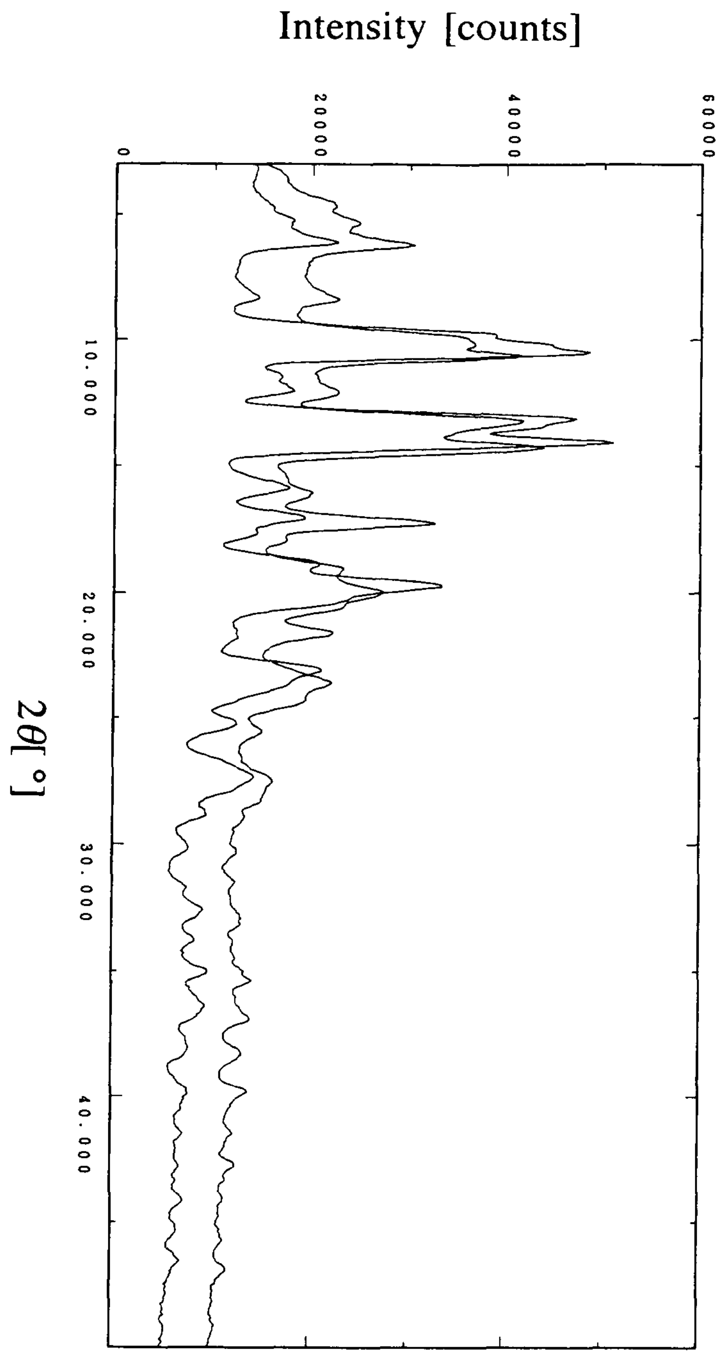


Fig. 2. X-ray diffraction patterns of the original (top) CA-3-FBzOH complex and of crystals heated to 333 K using CRTG (bottom).

To confirm that the adsorbed fluorobenzyl alcohols cannot be easily removed by filter paper, we washed the CA-3-FBzOH and CA-AP crystals as reference in diethyl ether for one minute using a mechanical stirrer and measured the CA-volatile substance ratio of the resulting crystals using conventional TG. If the loss is merely due to wetness, all the adsorbed molecules should be removed by this washing. The results are shown in Table 3. The weight loss of CA-AP does not change after the washing and the loss agrees well with the theoretical value (25.5 wt%) based on 1:1 complexation [10], whereas the CA-3-FBzOH complex reveals a larger weight loss than the theoretical value even after the washing. This result shows that many adsorbed molecules still exist on the surfaces. Consequently, 3-FBzOH molecules bind to the surfaces and to each other through weak interactions which are not easily broken, at least not by diethyl ether washing.

These experiments also suggest the substance release mechanism when the crystals of the CA-3-FBzOH complex were heated using CRTG. To begin with, only the adsorbed molecules are released at 330 K. As a result of this, the crystals become bare of "coating" molecules. Further heating causes the release of the included molecules at 346 K. The release reaction of the included molecules will now be described. Here it may be worth pointing out, in passing, the significance of the adsorbed molecules. When the X-ray analysis of the heated crystal was performed as described in a previous section, we found that the transparent crystal became opaque within a few days, unlike the original. Needless to say, X-ray reflection was no longer observed at this time. Thus we may assume that the adsorbed molecules contribute to crystal stability by coating.

From the previous discussion, it is reasonable to suppose that the adsorption on the surfaces is related to the properties of the fluorobenzyl alcohols. The fluorobenzyl alcohols have two "functional groups", an F atom and a CH_2OH group. To investigate the role of these functional groups in the adsorption, we performed thermal analyses on the crystalline complexes of CA with BzOH and 3′-FAP using conventional TG. The former has a CH_2OH group, but not an F atom, whereas the latter has an F atom at the *m*-position and a $COCH_3$ group instead of a CH_2OH group. Fig. 3(a) shows that a gradual weight loss occurs from 333 to 393 K when the crystals of CA-BzOH were heated. The total weight loss (38.4 wt%) corresponds to a host–guest ratio of 1:2.4 if all the loss is attributed to the release of the included guests. This ratio is, however, unlikely, judging from the fact that all the CA inclusion complexes whose structures have been elucidated by the X-ray method have a host–guest ratio of 1:1, 1:1.5 or 1:2

Table 3
Total weight loss[a] measured using conventional TG (in wt%)

Sample	CA-3-FBzOH	CA-AP
Original[b]	43.6	25.7
Washed[c]	38.4	25.5

[a] Up to 473 K.

[b] Dried with filter paper.

[c] Washed with diethyl ether and dried with filter paper.

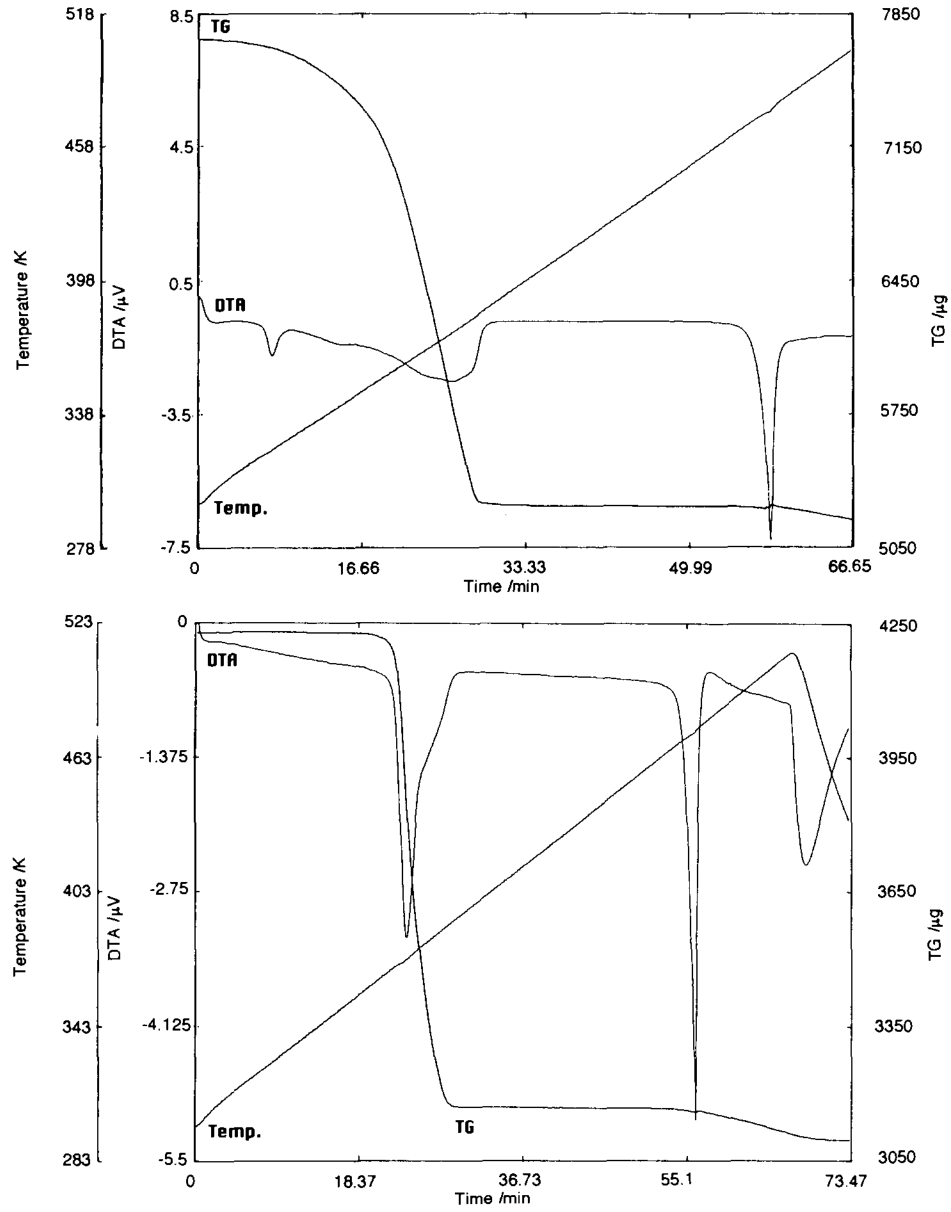


Fig. 3. Conventional TG plots of (a) CA-BzOH and (b) CA-3′-FAP.

[6,9–11,13–17]. Consequently, part of the weight loss may be attributed to the adsorbed BzOH molecules on the crystal surfaces. This measurement also suggests that the CH_2OH group contributes to the adsorption and that the F atom is not always necessary when substances adsorb on the surfaces. The TG curve for CA-3′-FAP is

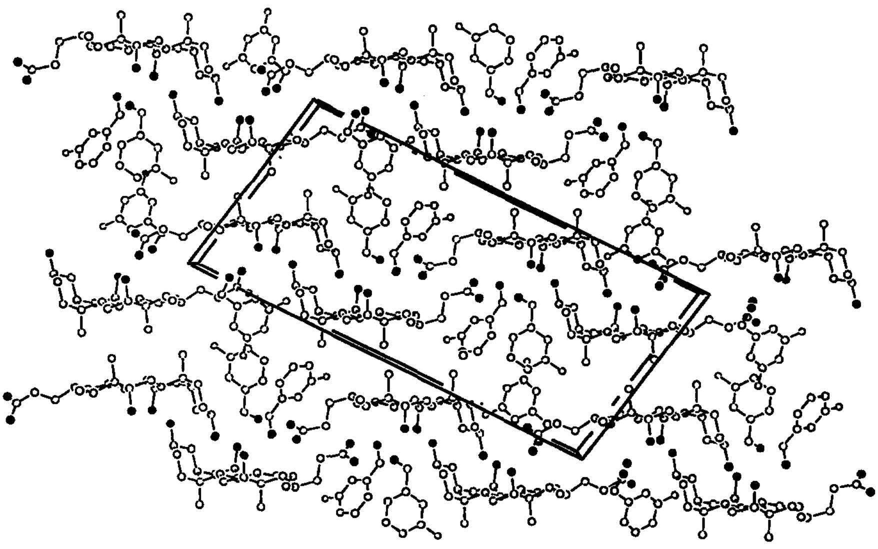


Fig. 4. Crystal structures of the CA-3-FBzOH inclusion complex viewed down the crystallographic *b*-axis. Carbon and oxygen atoms are represented by open and solid circles, respectively. Fluorine atoms are also represented by open circles [9].

depicted in Fig. 3(b), which shows a gradual weight loss from 361 to 388 K. The total weight loss (25.3 wt%) agrees well with the theoretical prediction (26.8 wt%) based on a host–guest ratio of 1:1 determined by the X-ray method [11]. This result shows that no molecules adsorb on the crystal surfaces, indicating that neither the F atom nor the $COCH_3$ group contribute to the adsorption. Thus the adsorption of the fluorobenzyl alcohols may depend on some properties of the CH_2OH group.

Next we discuss the included 3-FBzOH molecules. In a previous paper [9], it was described how CA molecules are grouped to form channel-like spaces, in which guest molecules are firmly accommodated (see Fig. 4). It is noteworthy that there are three kinds of crystallographically non-equivalent guest molecules and, therefore, the environment around a guest, including van der Waals contact and hydrogen bonding pattern, is different for each. In spite of such non-equivalence, only a single weight loss, except losses corresponding to the release of the adsorbed molecules, was observed at 346 K (see Fig. 1). This shows that the three kinds of guests are released at the same temperature. This is probably because the crystal lattice is broken at 346 K.

So far, we have described the adsorbed and included molecules. Here the crystal surfaces are discussed. Fig. 4 shows that several OH and COOH groups are widely distributed in a unit cell. So, it is reasonable to suppose that many polar groups exist on the crystal surfaces, although we have not determined which plane index each crystal surface belongs to. These polar groups would hydrogen-bond to the CH_2OH groups of the benzyl alcohols and the molecules would form the hydrogen bond networks on the crystal surfaces.

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